REMARKS

Claims 1, 10-11 and 13-14 are pending. Claims 2-9 and 12 are canceled. Claims 13 and 14 are new. Claims 1 and 11 are amended. Support for these amendments and new claims may be found throughout the Specification as filed. In particular and with references to US2007/0010430, amended claim 11 is supported at least by [0069] and [0088]; new claim 13 is at least supported by [0123]-[0128]; new claim 14 is supported at least by [0055].

Outstanding Issues:

- Claims 1-12 are rejected under 35 U.S.C. 112 ¶ 1 as lacking adequate written description to support the claims.
- Claims 1-10 and 12 are rejected under 35 U.S.C. 102(a) as anticipated by Murata (J. Nara Med. Assoc., V53(No. 5-6), December 2002.
- Claim 11 is rejected under 35 U.S.C. 102(e) as anticipated by WO03/068249 A1.
- Claims 1-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Murata in view of WO03/068249 A1.

I. Claims 1-12 are rejected under 35 U.S.C. 112 ¶ 1 as lacking adequate written description to support the claims.

A. Claim 11

The Examiner maintains the rejections against claims 11 for lack of sufficient written description as to the composition of the extract fraction produced by the method of claim 11. As the Examiner correctly states in the first office action, written sufficiency is defined by what is claimed and the specification must show possession of the claimed subject matter on the effective date of the application. Office Action mailed 14 November 2006, page 5. Claim 11 is a method with steps. Each step is explicitly reduced to practice in the specification:

pulverizing shark cartilage into a pulverized product with an average particle diameter of 100 μm or less in liquid nitrogen [0088],

adding water to the pulverized product of the preceding step a) and extracting water-soluble components from it, [0088],

separating an aqueous phase that contains the extracted water-soluble components [0088];

partially separating and removing extracted water-soluble components below 6 kDa [0088],

adding an alcohol to the aqueous phase to produce a precipitate [0088],

gel filtration purification of the precipitate to isolate the extracted water-soluble components having a gel filtration estimated molecular weight of 500 kDa or more [0104], and

selecting gel filtration fractions correlated with a MMP-9 inhibition activity and a MMP-2 inhibition activity [FIG. 8].

B. Claims 1 and 10

Applicant submits that, as discussed in the interview of 11 Sept. 2007, the pending composition claims are not directed to a specific biomolecule but rather to a composition defined by source materials and specific biophysical characteristics. Because Applicant is not claiming a biomolecule *per se*, the pending Written Description rejection is inapplicable to the presently presented claims. The Written Description requirement is that the specification convey to one of ordinary skill in the art that the Inventors had possession of the claimed subject matter as of the filing date of the application. The application clearly conveys possession by the Inventors of the claimed gel filtration fraction, [Figure 8A-B], derived from shark cartilage, [0041] and [0088], having the claimed aggregate amino acid composition, [Figure 2], chondroitin sulfate C content, [Figure 7], and other claimed biophysical properties, [0079], [0080] and [0088].

Because the Written Description requirement is clearly met by the presently presented claims, Applicant respectfully requests the rejection be withdrawn.

II. Claims 1-10 and 12 are rejected under 35 U.S.C. 102(a) as anticipated by Murata (J. Nara Med. Assoc., V53(No. 5-6), December 2002.

Applicant submits herewith the declaration of Nao Murata under 35 CFR 1.132 to prove that, Murata, "Effects of Bovine and Shark Cartilage Water Extracts on Pancreatic Ductal Carcinogenesis in Hamsters," Journal of Nara Medical Association, 53(5-6): 241-252, 2002, is not available as prior art under 35 U.S.C. 102(a).

During the in person interview of 11 Sept. 2007, there was some confusion regarding the requirements for the declaration's contents. The requirement for conception/reduction to practice dates and activity in a WTO country relate to declarations under 37 CFR 1.131 to "swear in back of" a publication. *See* MPEP 715. The presently submitted declaration establishes that the cited reference constitutes Applicant's own work and thus may not serve as a basis for rejection under 102(a). *See* MPEP 2132.01; *In re Katz*, 687 F.2d 450, 454 (CCPA 1982); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1380-81 (Fed. Cir. 2005):

> The basic tenet of U.S. patent law is that an original inventor gains an exclusive right to the invention. U.S. Const. art. I, § 8, cl. 8. Thus, an inventor's own work cannot be used to invalidate patents protecting his own later inventive activities unless, *inter alia*, he places it on sale or uses it publicly more than a year before filing. 35 U.S.C. § 102(b); see also In re Katz ,687 F.2d 450, 454 (CCPA. 1982); In re Facius, 56 C.C.P.A. 1348, 408 F.2d 1396, 1406 (CCPA 1969) ("Certainly one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar.")

Applicant respectfully requests the rejection be withdrawn.

Applicant however must point out that the Examiner may be mistaken as to the eligibility of Murata as prior art under 102(b). To Applicant's knowledge, the foreign priority date for the JP parent application of the priority PCT application is not the effective U.S. filing date because U.S. law has not been amended to comply with the Paris Convention or the PCT. Consequently, the effective date from which on calculates the one year grace

period of 102(b) is the PCT application filing date. Applicant requests the Examiner revisit this issue and confirm the applicable statutory provisions.

Applicant submits that the availability of Murata as prior art is no longer relevant due to the claim amendments made herein. The pending process claim now includes limitations to pulverizing the shark cartilage in liquid nitrogen, partially separating and removing extracted water-soluble components below 6 kDa, and selecting gel filtration fractions corresponding to estimated molecular weights of 500 kDa or more and correlated with MMP-9 & -2 inhibition activity. Applicant submits Murata is clearly not anticipatory of the present claim because none of these limitations are present. The pending composition claims relate to a gel filtration fraction having a defined amino acid composition and other biophysical properties. Murata again does not disclose elements corresponding to these limitations and thus is not anticipatory.

Because Murata is not available as prior art under 102(a) and is not anticipatory of the pending claims, Applicant respectfully requests the rejection be withdrawn.

III. Claim 11 is rejected under 35 U.S.C. 102(e) as anticipated by WO03/068249 A1.

The pending process claim now includes limitations to pulverizing the shark cartilage in liquid nitrogen, partially separating and removing extracted water-soluble components below 6 kDa, and selecting gel filtration fractions corresponding to estimated molecular weights of 500 kDa or more and correlated with MMP-9 & -2 inhibition activity. Applicant submits Kralovec is clearly not anticipatory of the present claim because none of these limitations are present.

Applicant respectfully requests withdrawal of the rejection.

IV. Additional SIPO cited art under 35 U.S.C. § 102(b)

In the interest of expediting examination, Applicant addresses the newly cited, English language references and translations of Chinese language references identified by SIPO.

The abstract to and partial translations of the LI Dong-xia et al. reference indicates the compositions therein contain the acid mucopolysaccharide component of shark cartilage and only trace amounts of protein. Thus, the LI Dong-xia et al. compositions appear unrelated to the presently claimed compositions. Applicant's attorney was able to confirm this by finding the Chinese language document and translating it through the free Google translator software (co-submitted). While not perfect, the translation is clear enough to show that the methodology applied to purifying SCAMP is quite unrelated to the pending claims as is the resultant product.

The abstract to the ZHU Xiang-rong et al. reference indicates that the paper relates to seawater corrosion and is thus unrelated to the pending claims.

The abstract of CN1182539 discloses a pesticide composition which is not related to the claimed compositions. The partial translation indicates the process is directed at producing a protein free chondroitin sulfate composition unrelated to the pending claims.

The partial translation of CN1031087A relates to saponin isolation from plants and is completely unrelated.

WO97/16197 does not disclose a step of selecting gel filtration fractions correlated with MMP-9 and -2 inhibition activity among many described properties. *See, e.g.*, Pg. 7, lines 15-26; Pg. 24 and 31 (cancer cell line proliferation assay); Pg. 27 (tumor growth inhibition *in vivo*); Pg. 38 (collagenase activity); Pg. 44 (anti-inflammatory activity). Nor does WO97/16197 disclose gel filtration fractions having the claimed amino acid composition. Pg. 16, line 5- Pg. 19, line 25; Figure 1. At least based on these distinctions, WO97/16197 does not anticipate the presently presented claims.

WO00/04910 discloses an aqueous extraction process followed by a size separation step to isolate "cartilage molecules having molecular weights less than about 500 kDa." Pg. 13, lines 10-26; Pg. 16, lines 13-31. These processes do not involve pulverizing the cartilage in liquid nitrogen. Additionally, these processes do not use gel filtration to isolate molecules of 500 kDa or more in size. WO00/04910 thus does not anticipate the pending process claim 11. Because the protein composition of shark cartilage water extracts will be distinct

between the two size ranges (0-about 500 kDa vs. 500 kDa and up), the aggregate amino acid composition limitation of claim 1 distinguishes it from the fractions disclosed by WO00/04910.

V. Claims 1-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Murata in view of WO03/068249 A1.

In view of the additional SIPO cited art and the possible availability of Murata under 102(b) , Applicant addresses the above references collectively for compliance with 35 U.S.C. § 103(a).

Initially, as discussed above, the ZHU Xiang-rong et al. reference, the LI Dong-xia et al. reference, CN1182539 and CN1031087A all relate to radically differing processes and resultant compositions. These references are focused on non-protein, small molecule compounds and various harsh extraction/purification conditions unrelated to the pending process claims or the pertinacious gel filtration fractions claimed.

Murata is not anticipatory of the pending claims as detailed above. Murata does define the state of the art prior to the present disclosure. Murata confirms that water extracts of shark cartilage possess MMP-9 and MMP-2 inhibiting properties. *E.g.* Figure 2. Murata further indicates these extracts should be analyzed for the active component(s). *See* Discussion, first paragraph. Murata speculates the activity is correlated with chondroitin C, either free or bound to proteoglycans, and that the bioavailability of orally administered chondroitin C may explain the reported animal oncology experiments' results. *Id.*

Kralovec is distinguished as discussed above for the 102(e) rejection. The pending process claim now includes limitations to pulverizing the shark cartilage in liquid nitrogen, partially separating and removing extracted water-soluble components below 6 kDa, and selecting gel filtration fractions corresponding to estimated molecular weights of 500 kDa or more and correlated with MMP-9 & -2 inhibition activity. None of these limitations are present in Kralovec. Kralovec largely describes immune cell proliferation and cytokine production stimulation using "fraction 4." *See* Figures 5-9. "Fraction 4" is a lyophilized total water extract of pulverized shark cartilage dialyzed against a 12 kDa membrane. Pg. 20. In

addition, the amino acid composition of the Kralovec compositions is distinct from those encompassed by the pending claims. Pg. 8, lines 10-20. Thus these results with "fraction 4" do not relate to the claimed MMP-9 inhibiting gel filtration compositions or the process of producing these compositions. Figure 1B is different. Here, "fraction 4" has been split by utrafiltration into size ranges with the most potent fraction for stimulating immune cell proliferation identified as the greater than 1 mega Dalton size fraction. This correlation between high molecular weight components and immune cell proliferation does fairly suggest that these higher molecular weight fractions are of interest for immunostimulating components. Applicant contends that stimulating immune cell proliferation and/or cytokine production are not logically related to MMP-9 or -2 protease inhibition or components capable of such inhibition.

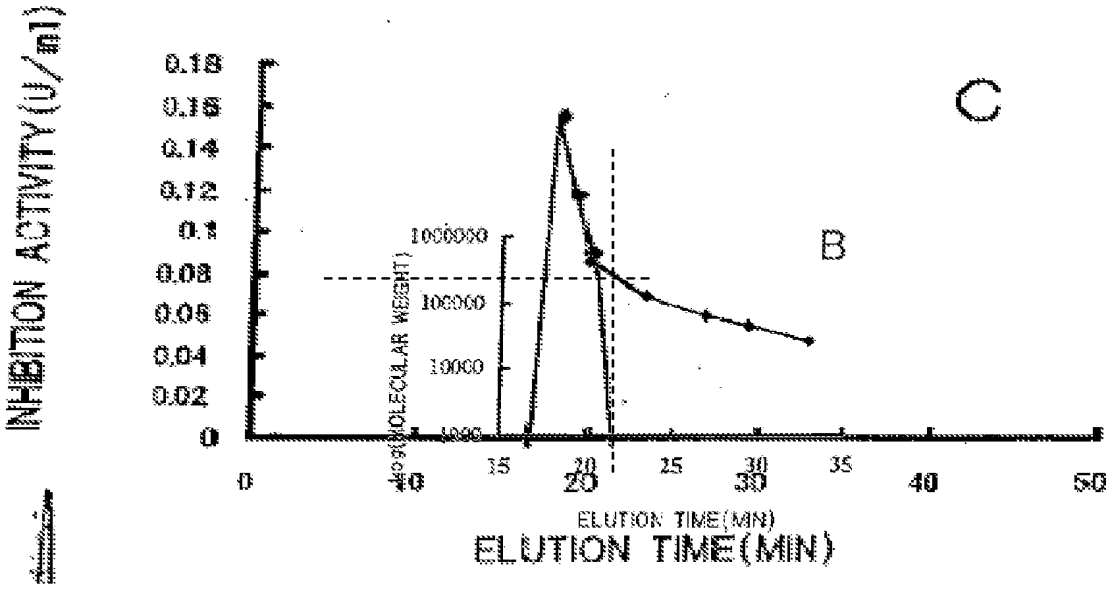
Viewed from as a collective from the perspective of one of skill in the art, the foregoing literature identifies some properties of interest in gel filtration fractions overlapping with the claimed size range and some of the steps used in the claimed processes. Applicant contends taken as a whole, the pending, very focused claims are not rendered obvious by the forgoing art.

A. WO00/04910 and WO97/16197

WO00/04910 incorporates the contents of WO97/16197 (along with earlier applications). Pg. 16, lines 13-17. These disclosures should therefore be read together as a collective. WO00/04910 + WO97/16197 discloses pulverizing shark cartilage, water extraction followed by size separation to derive 0-1 kDa, 0- about 500 kDa and 1- about 500 kDa fractions. WO00/04910 specifically identifies MMP-2 inhibition activity in these fractions. *E.g.*, pg. 19, Table 6 (GIA = MMP-2). WO00/04910 + WO97/16197 do not disclose or suggest pulverizing the shark cartilage in liquid nitrogen and there is no basis for modifying the references to do so. *E.g.*, WO97/16197 at pg. 8, lines 23-25; pg. 17, lines 9-26; pg. 18, lines 10-17.

WO00/04910 + WO97/16197 do disclose MMP-2 inhibition determination of size separated extract fractions which overlap in size with the presently claimed size range (0-about 500 kDa vs. 500 kDa and up). *See* MPEP 2144.05.

Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing "(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art." *See* MPEP 2144.05 (III.). The main fraction of WO00/04910 + WO97/16197 is a 0-500 kDa produced by tangential flow filtration with a 500 kDa cut off membrane. WO97/16197 at pg. 19, first paragraph. Thus the starting point for WO00/04910 + WO97/16197 is to exclude the size range specifically claimed herein and which encompasses the MMP-2 & MMP-9 inhibition activity associated with the claimed size fractions (FIGURE 8 - B & C superimposed):



WO00/04910 goes on to focus on the 0-1 kDa size range because it has the highest degree of MMP-2 activity. Pg. 19, Table 6; pg. 26, Table 7. Finally, WO00/04910 discloses a 284 Dalton, non-protein molecule (AE-986) as the active species for MMP-2 inhibition. Pg. 27-32. WO00/04910 does speculate that some other component(s) within the 1-500 kDa size fraction also may have MMP-2 inhibition properties. Pg 20, lines 1-20. This speculation is muddied somewhat by the fact that the so-called 1-500 kDa fraction is in fact R6-1-500 from Table 5 (pg. 17) and still contains some 0-1 kDa materials, including presumably some AE-986. However, subsequent research with the fractions of WO00/04910 identified

additional TIMP-1 and -3 related molecules in the 20-35 kDa size range having some MMP inhibiting activity. *See* Gingras, D., et al., Matrix Proteinase Inhibition by AE-942, a Multifunctional Antiangiogenic Compound, Anticancer Research 21: 145-156 (2001). Applicant submits WO00/04910 and related literature would not lead one of skill in the art to derive the shark cartilage extract processing steps for producing MMP-2 inhibiting, gel filtration fractions of (1) partially removing components of less than 6 kDa (i.e. AE-986) and (2) size separating and discarding components of less than 500 kDa (i.e. the size range specifically selected for in WO00/04910 + WO97/16197). Likewise, the protein constituents, and thus the amino acid composition, of the 0-1, 0-500 and 1-500 kDa fractions in WO00/04910 + WO97/16197 will be distinct and nothing in WO00/04910 + WO97/16197 would lead one of skill in the art to produce the claimed gel filtration fraction compositions having the amino acid composition in Figure 2.

Comparing WO00/04910 + WO97/16197 with Kralovec, does not change the analysis. Art should be viewed collectively for what it fairly discloses on balance. MPEP 2143.01(II). The information on Kralovec regarding higher molecular weight fractions having immune cell proliferation stimulating properties does not relate to or inform one of MMP-2 or MMP-9 protease inhibition properties. In contrast, WO00/04910 + WO97/16197 is focused on identifying MMP-2 inhibiting components. The specific and directly related contents of WO00/04910 + WO97/16197 should therefore be the controlling evidence on the issue of obviousness.

Claim 11 also requires a step of pulverizing shark cartilage in liquid nitrogen. One of skill in the art would not reasonable expect that this process would produce materials from which MMP-2 and MMP-9 activity could be derived. MPEP 2143.02 (Reasonable Expectation of Success Is Required). For example, WO97/16197 specifically warns that pulverization similar to that in the claimed processes may be deleterious to biological activities of resultant products:

> obtention of the first grinded cartilage equally apply. The size of the particles after homogenization does not need to be ultra small. Therefore, the need to pulverize the cartilage before extraction can be avoided. Indeed, pulverization of cartilage in the form of a powder before aqueous extraction may on the contrary denature valuable activities, specially when such pulverization is performed in a freeze-dry state and/or in a heat-dry state.

Pg. 18, lines 10-17. The information regarding the unrelated biological activity of the fractions disclosed by Kralovec does not inform one of skill in the art regarding whether MMP-9 or MMP-2 enzyme inhibition activity might survive the pulverization used therein. Pg. 18, lines 21-26. Taken as a whole, the art does not support the position that one would reasonably expect the claimed processes to work.

Because the references cited by SIPO and the art of record as a whole do not render the pending claims obvious, Applicant respectfully requests the claims be allowed.

In view of the above amendment, applicant believes the pending application is in condition for allowance. Three month's extension of time is requested and the fee therefore co-submitted with this response. Applicant believes no other fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P03167US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

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